REMARKS

Claims 26, 27 and 29-36 are currently pending and under consideration in the above-identified application.

Applicants gratefully acknowledgment the withdrawal of all the objections and rejections, except for the rejection under Section 103 discussed below, set forth in the previous Office Action mailed May 7, 2001.

REJECTION UNDER 35 U.S.C. § 103(a)

Claims 26 and 27 remain rejected and claims 29-36 are newly rejected under 35 U.S.C. § 103(a), allegedly, as obvious over U.S. Patent No. 5,686,432 to Baggio et al. ("Baggio") in combination with U.S. Patent No. 5,252,339 to Cristofori et al. ("Cristofori") and U.S. Patent No. 5,496,807 to Marchi ("Marchi").

Applicants respectfully disagree with the Examiner's rejection. Cristofori teaches a pharmaceutical composition for oral administration of 25 to 500 mg of glycosaminoglycans, including but not limited to sulodexide, in the form of a gastro-resistant coated formulation. However, Cristofori does not teach or suggest the administration of sulodexide for the treatment of diabetic nephropathy. Cristofori teaches that the administration of sulodexide is for the "prevention and treatment of thrombotic and atherosclerotic pathologies" (column 2, lines 50-51) and that administration of sulodexide is in such manner for "best performance of the anticoagulant, fibrinolitic antithrombotic, antitherosclerotic and antihyperlipoproteineic activities" (column 2, lines 55-58). This publication is completely silent as regards diabetic nephropathy.

Marchi teaches dosages of 500 to 1500 LRU sulodexide per day to treat diabetic nephropathy, which is equivalent to 50 to 150 mg per day. Marchi does not teach a method for treating diabetic nephropathy by administering more than 150 mg sulodexide per day. In fact, Marchi administered only either (a) two capsules containing 250 LRU (25 mg)

twice a day (column 3, lines 10-16 and column 4, lines 24-26 of Marchi); or (b) an injection of 600 LRU (60 mg) once a day (column 3, lines 35-40). This publication only provides evidence from clinical trials where the amounts of sulodexide administered are approximately one-fourth of the minimal amount taught and claimed in the present application.

With regard to the teachings of Baggio, Applicants respectfully submit that the Examiner has misinterpreted the teachings of Baggio. Baggio does not teach the use of sulodexide for preventing and curing of nephropathy caused by diabetes by fighting against the phenomena that causes alteration in renal structure and function. A citation to this use is found at column 1, lines 59-69 of Baggio; however, this citation refers to EP 0624374, which is the European counterpart of Marchi, discussed above.

Baggio actually teaches administering sulodexide to improve the performance of CAPD (Continuous Ambulatory Peritoneal Dialysis) by lowering the protein loss in the dialytic liquid thereby preventing structural and functional alterations of the peritoneal membrane by improving the capability and the selectivity of the filtration of the peritoneal membrane (*e.g.*, column 1, lines 14-15, column 2, lines 60-64). Thus, the method taught by Baggio is to treat patients undergoing ambulatory dialysis by administering directly to the peritoneum a dialysis liquid containing sulodexide. Baggio teaches that sulodexide is intended to prevent or slow the deterioration of the peritoneal membrane by local administration to the peritoneal cavity. Sulodexide is not intended to work in the kidney and, in fact, cannot do so since the mode of administration taught by Baggio does not place sulodexide in the circulatory system so that sulodexide can reach the kidney.

Furthermore, although Baggio discloses administering a maximum of 500 mg of sulodexide intraperitoneally, a reading of the actual clinical trial set forth in Example 4 shows that the actual dosage used was only 50 mg of sulodexide administered in a single nocturnal exchange of the fluid (column 5, lines 64-66), which amount of sulodexide was further diluted by the additional four washes with dialysis liquid without sulodexide.

The Examiner's rejection appears to allege that combining Baggio (teaching of administrations of high dosages of sulodexide to the peritoneal cavity) with Cristofori (teaching of oral administration) and Marchi (teaching of treatment of diabetic nephropathy by oral administration of low dosages of sulodexide) would have allowed one of skill to arrive at the presently claimed invention. However, the Examiner mistakenly extrapolates dosages for oral (systemic) administration from dosages used in peritoneal delivery. The Examiner fails to take into account the well known anti-thrombosis activity of sulodexide, which is a concern where sulodexide is administered systemically, *i.e.*, enters the blood stream. Such a concern is not relevant with peritoneal administration of sulodexide, since peritoneal administration does not permit sulodexide to enter the blood stream. Moreover, Applicants note that Baggio did not administer more than 50 mg/day sulodexide. It would appear that such dosage was further diluted by the additional four washes without sulodexide.

Thus, Applicants respectfully submit that those of skill in the art would not have extrapolated the teachings of Baggio to oral administration since the distribution of sulodexide in the body administered to the peritoneum is substantially different from the distribution of sulodexide administered orally. Thus, one skilled in the art would not take Baggio as a teaching that high dosages of sulodexide can be administered orally. Further, the teachings of Cristofori (oral administration) and/or Marchi (treatment with low doses) do not fill in the gap. A rejection for obviousness is improper when there is nothing in the cited combination of prior art references to motivate a combination of their teaching or to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473

(Fed. Cir. 1988). Applicants respectfully submit that none of the cited references provide the required suggestion or expectation to render obvious the claimed invention.

Moreover, Applicants submit, as taught in the specification on page 8, lines 7-35, that daily oral administration of 200 mg sulodexide improved the therapeutic effects of sulodexide (75% reduction of AER as compared to 50% reduction using 100 mg sulodexide during the experiment period) and maintained the beneficial effects for a longer period of time (maintenance of 65% reduction of AER with the 200 mg daily dosage, as compared to maintenance of 28% with the 100 mg daily dosage as measured at 4 months after termination of the trial). Thus, a higher dosage of sulodexide have a significantly better therapeutic index and a significantly longer period of therapeutic effect, without adverse side effects, as compared to a dosage of 100 mg per day.

Applicants further note that with regard to the Examiner's comment that a declaration or affidavit is required for support of an argument of unexpected results, it is the inventors themselves in the specification on page 7, lines 20-21 that characterize the results as unexpected, and thus, such characterization cannot be considered to be solely attorney argument.

Therefore, in view of the foregoing, Applicants respectfully submit that the Section 103 rejection has been overcome, and thus, Applicants respectfully request that the rejection be withdrawn.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Applicants note that a Supplemental Information Disclosure Statement is submitted concurrently herewith. Applicants request that the Examiner review the cited references and make them of record in the present application.

CONCLUSION

Applicants respectfully request that the remarks of the present response be entered and made of record in the present application. Claims 26, 27 and 29-36 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejection and allowance and action for issuance are respectfully requested.

Applicants request that the Examiner call Geraldine F. Baldwin at (212) 790-2296 if any questions or issues remain.

Respectfully submitted,

Date: June 17, 2003

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Enclosures